

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No: 37974-0189

In re patent application of

TESCHNER, Wolfgang *et al.*

Confirmation No.: 6758

Serial No.: 09/254,288

Group Art Unit: 1651

Filed: April 2, 1999

Examiner: Irene Marx

For: PROCESS FOR PRODUCING A PLASMA PROTEIN-CONTAINING
MEDICAMENT

DECLARATION OF WOLFGANG TESCHNER

I, Wolfgang Teschner, do hereby declare as follows:

1. A copy of my *curriculum vitae* has been previously provided. I provide the following declaration to address the rejections made by the examiner in U.S. Serial No. 09/254,288.

2. U.S. Patent No. 5,946,930 describes that the increase of dissolved aluminum observed during storage of albumin in glass containers is related to the citrate concentration of the preparation. Example 1 of the '930 patent alleges that by dissolution of fraction V obtained by the Cohn fractionation process and diafiltration followed by adjustment to a 20% protein concentration a citrate concentration can be reached which is sufficiently low for keeping the aluminum level below a limit of $\leq 200\mu\text{g/l}$ throughout the storage. The '930 patent further alleges that the citrate concentration should be less than 0.12 mmol/l in order to reach this target. The following study, however, shows that mere diafiltration of fraction V (dissolved in sodium chloride solution) against water for injection (WFI) is not sufficient to obtain low citrate concentrations as alleged in the '930 patent.

3. In contrast to the '930 patent, addition of caprylate to a fraction V solution, which is able to replace the citrate bound to the albumin, and subsequent diafiltration is capable of reducing the citrate content of the preparation. This approach is not described in the '930 patent, but is rather disclosed only in the U.S. Serial No. 09/254,288. The below experiment demonstrates the efficacy of applicants' approach, and the advantages it possesses over the disclosure of the '930 patent/

4. The starting material was the albumin precipitate V from cold ethanol fractionation lot A01296. In the experiments, the same lot was used in order to assure ideal comparability. This precipitate consists of more than 95% albumin, which is required by the European Pharmacopoeia for an Albumin final container.

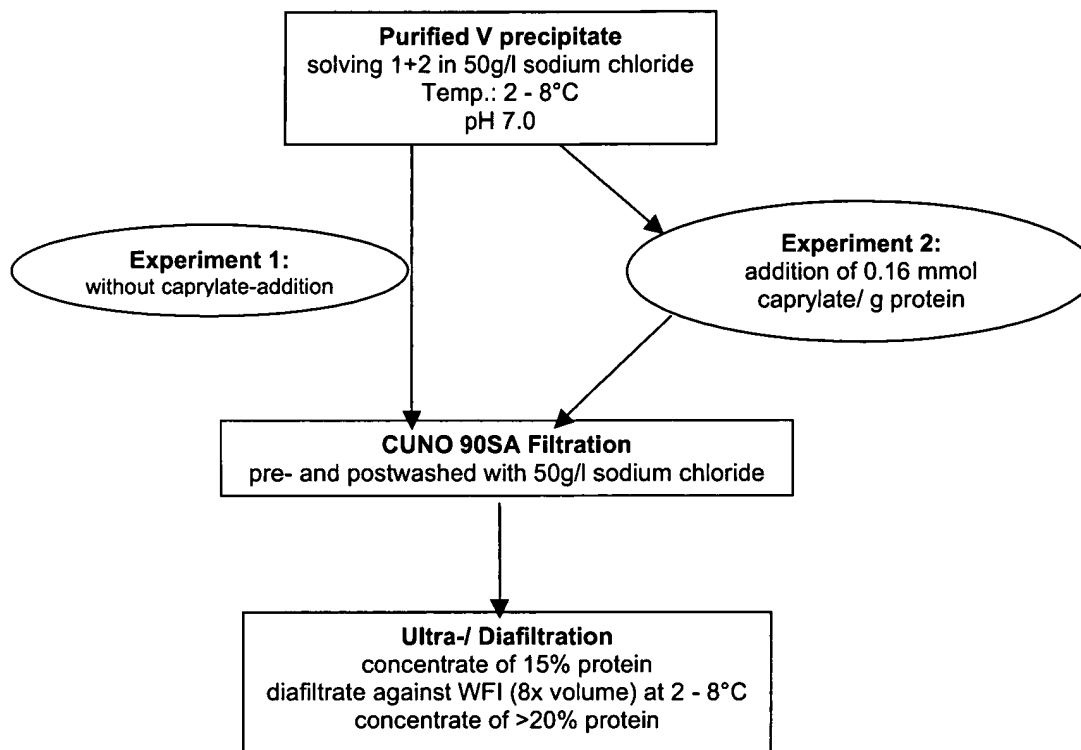
5. Experiment 1: without caprylate-addition

Fraction V precipitate was dissolved 1+2 in 50g/l sodium chloride at 2 – 8°C. The pH was adjusted to 7.0 during stirring. After dissolving, the suspension was filtered through Cuno 90SA at 2 – 8°C. The filter was pre- and post-washed with 50g/l sodium chloride. The pressure during the filtration was 1bar. After the filtration samples were drawn and analyzed for protein, citrate and aluminum content. This filtrate was concentrated to 15% protein by using an ultrafiltration membrane from Millipore (CDUF001LD 10K; regenerated cellulose; #P5JM0169). Then, the concentrate (15% protein) was diafiltrated against water for injection (8x) at 2 – 8°C. After diafiltration the protein was further concentrated to a protein value of about 20%. This concentrate was tested for protein, citrate and aluminum content.

6. Experiment 2: caprylate-addition before Cuno-Filtration (0.16 mmol caprylate/ g protein) in order to replace citrate

Similar to Experiment 1 described above, fraction V precipitate was dissolved 1+2 in 50g/l sodium chloride at 2 – 8°C. The pH was adjusted to 7.0 during stirring. The suspension contained 72.94g of protein. To this suspension, 0.16 mmol caprylate/ g protein was added. See page 9 of U.S. Serial No. 09/254,288. After addition of the caprylate, the suspension was filtered through Cuno 90SA at 2 – 8°C as described in Experiment 1. The filter was pre- and post-washed with 50g/l sodium chloride. The pressure during the filtration was 1bar. After the filtration samples were drawn and analyzed for protein, citrate and aluminum content. The filtrate was concentrated at 15% protein by using the same ultrafiltration membrane from Millipore (CDUF001LD 10K; regenerated cellulose; #P5JM0169). Then the concentrate (15% protein) was diafiltrated against water for injection (8x) at 2 – 8°C. After diafiltration, the protein was concentrated to a protein value of about 20%. The concentrate was tested for protein, citrate and aluminum content.

7. Experiments 1 and 2 are schematically depicted in the below flow chart:



8. The following results were obtained:

Experiment 1:	Fraction V dissolved after clarification			Concentrate		
	protein	citrate	aluminum	protein	citrate	aluminum
	%	mmol/l	µg/l	%	mmol/l	µg/l
measured values	8.28	12.78	321	18.68	0.99	21.9
Values normalized at 20% protein	20.00	30.87	775	20.00	1.06	23.4

reduction of citrate: 96.6%
reduction of aluminum: 97.0%

Experiment 2:	Fraction V dissolved after clarification			Concentrate		
	protein	citrate	aluminum	protein	citrate	aluminum
	%	mmol/l	µg/l	%	mmol/l	µg/l
measured values	8.47	12.20	355	18.58	0.04	<3.5
Values normalized at 20% protein	20.00	28.81	838	20.00	0.04	<3.8

reduction of citrate: 99.9%
reduction of aluminum: 99.5%

9. Experiment 1 shows, that diafiltration against WFI (8 times) is not sufficient to obtain a citrate concentration sufficiently low to assure that the limit of $\leq 200 \mu\text{g/l}$ aluminum is not exceeded during storage of the product. When normalized to 20% protein concentration, a residual citrate concentration of 1.06 mmol/l was measured, which is far above the citrate concentration of less than 0.12 mmol/l described in the '930 patent. In contrast, the conditions described in U.S. Serial No. 09/254,288 provide for a citrate concentration of less than 0.12 mmol/l. When normalized to 20% of protein, the value of the residual citrate concentration in the preparation was 0.04 mmol/l.

10. The above experiments show that the replacing of citrate by a water-soluble monocarboxylate, a water-soluble dicarboxylate, a monocarboxylic acid or a dicarboxylic acid (caprylate is an example) is responsible for the attainment of a medicament that is and will remain substantially free of undesired metals. This replacement of citrate is simply not taught or suggested by the '930 patent, and therefore the '930 patent will not provide the medicaments that are provided by U.S. Serial No. 09/254,288.

11. U.S. Patent No. 5,561,115, cited by the examiner, also is deficient. As I explained in paragraphs 6-7 and Appendix B of my declaration dated June 3, 2002, the '115 patent does not use caprylate to replace citrate. Rather, the '115 patent uses caprylate as an agent for precipitating unwanted proteins or is present in the final container for maintaining the product stability. Accordingly, the '115 patent does not teach or suggest the methodological steps disclosed by applicants in U.S. Serial No. 09/254,288, and therefore does not provide the medicaments provided by U.S. Serial No. 09/254,288.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

December 9, 2004

Wolfgang Teschner
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